REMARKS

Claims 1-14, 20, 21, 27-35 and 37 presently appear in this case. Claims 34, 35 and 37 have been allowed. Claims 2, 6, 12-14, 20, 21 and 27-33 have been objected to. Claims 1 and 7-11 are presently subjected to rejection. The official action of April 3, 2003, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to certain novel non-hemolytic cytotoxic peptides having a selective cytolytic activity such that they are much more toxic to pathogenic cells then they are to red blood cells. The peptide may be a cyclic derivative of a peptide having a net positive charge that is greater than +1 and comprising both L-amino acid residues and D-amino acid residues, or comprising only D-amino acid residues and having an α-helix breaker moiety. The peptide may also comprise both L-amino acid residues and D-amino acid residues, having a net positive charge which is greater than +1, and having a sequence of amino acids such that the same amino acid sequence in which each residue is in the L-configuration is not found in nature, and cyclic derivatives thereof. The peptides may also be a random copolymer consisting of a hydrophobic, a positively charged, and a D-amino acid. The claims exclude the peptides of SEQ ID NO:1, 12 and 14.

Claims 1 and 7 have been rejected under 35 USC 102(b) as being anticipated by Shai. The examiner states that Shai discloses the peptides designated (D)P^7 and (D)$L^{18}L^{19}$. The examiner says that Shai indicates that (D)P^7 is cytolytic at a concentration at which it is not hemolytic and that (D)$L^{18}L^{19}$ is also non-hemolytic at a cytolytic concentration. Thus, the examiner considers the claims to be anticipated by these compounds.

These peptides are the same as peptides 12 and 14 mentioned on page 26 of the present specification and in Table 1. Claim 1 has now been amended to exclude them in the proviso section. Accordingly, none of the present claims are anticipated by Shai. Reconsideration and withdrawal of this rejection is respectfully urged.

Claims 1 and 7 have been rejected under 35 USC 102(b) as being anticipated by Lakey. The examiner states that Lakey discloses analogs of the lipopeptide antibiotic A21978C, which is disclosed as being cytotoxic at much lower concentrations than it is hemolytic. The examiner states that the N-acyltryptophan in this compound is an amino acid which is not found in nature, and, given this interpretation, the peptide disclosed by Lakey meets all the requirements of the claims. This rejection is respectfully traversed.

The examiner's attention is drawn to the fact that another important feature of the peptide of claim 1(B) is a net charge which is greater than +1. At the first full paragraph on page 224, Lakey states:

> The peptide contains few non-polar amino acids and one of these, a tryptophan residue, sits at the top of the lipid chain. The rest of this acidic peptide must carry a clear amount of negative charge although the exact state of ionization of the groups is not known.

Thus, as A21978C is definitely an acidic peptide with a negative charge, it cannot be anticipated by claim 1, which requires a net positive charge which is greater than +1. Reconsideration and withdrawal of this rejection is therefore also respectfully urged.

Claims 1 and 7-11 have been rejected under 35 USC 103 as being unpatentable over Shai. The examiner states that Shai teaches compounds which are antibacterial but non-hemolytic, the exact sequences of which have been disclaimed by proviso. However, the examiner states that, when a side chain of one amino acid in a peptide is extended by one methylene unit, the biological activity of that peptide would be expected to remain substantially the same. Thus, the examiner considers the present claims to be *prima facie* obvious from the disclaimed compounds of Shai because they

read on adjacent homologs thereof. This rejection is respectfully traversed.

Shai does not disclose that if one of the amino acid side chains is extended by one methylene unit that cytotoxic activity will be retained. However, in the examiner's opinion, a peptide biochemist of ordinary skill would have expected *a priori* that the biological activity would remain the same if the side chain of one amino acid in a peptide is extended by one methylene unit.

Professor Yechiel Shai, a recognized expert peptide biochemist, explains that it is well known in peptide chemistry that small changes in the peptide molecule, e.g., by addition, deletion and/or replacement of one amino acid by another, even by adding or deleting a methylene unit, as suggested by the examiner, may abolish, reduce or augment the biological activity. If necessary, this opinion can be presented in the form of a declaration.

In the present invention two parameters are required. The peptide has to be cytolytic and non-hemolytic. Through small changes, it may be obvious that the peptide will conserve its cytolytic activity, but it is not obvious whether it will be hemolytic or non-hemolytic. In example 2 of the present application, it is shown that similar peptides are all cytolytic, but only some of them are non-hemolytic. Prior to

the present invention, it would not have been possible to predict whether or not any small changes to the compounds of Shai would remain non-hemolytic. Accordingly, no *prima facie* case of obviousness has been established. Reconsideration and withdrawal of this rejection is therefore respectfully urged.

It is submitted that all the claims now present in the case clearly define over the references of record and fully comply with 35 USC 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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